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ORIGINAL ARTICLE

Effects of dose ranging of adenosine infusion on electrocardiographic findings during and after general anesthesia

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Abstract
Purpose To assess changes in the electrocardiogram (ECG) associated with intraoperative infusion of adenosine in patients undergoing open abdominal gynecological surgery.
Methods One hundred and sixty-six patients undergoing gynecological surgery were randomly assigned to receive one of four doses of adenosine infusion (25, 50, 100, or 200 μg/kg/min) or matching placebo. Study drug administration was started at skin incision and discontinued at end of surgery. A standardized general anesthetic regimen was used and adjusted based on hemodynamic and bispectral index values. Heart rate and rhythm variables, and PR, QRS, QT, and QTc intervals were recorded from 12-lead ECGs before anesthesia and immediately after patient arrival in the postanesthesia care unit. In addition, a rhythm strip was obtained during administration of the loading dose of the study drug. ECG variables were compared within and between groups. Incidence of ECG and hemodynamic abnormalities was recorded.
Results One hundred and fifty-one subjects had a full set of electrocardiographic data: placebo ($n = 38$), group adenosine 25 μg/kg/min ($n = 31$), group adenosine 50 μg/kg/min ($n = 29$), group adenosine 100 μg/kg/min ($n = 28$), and group adenosine 200 μg/kg/min ($n = 25$). Statistically significant postoperative QTc prolongation was observed in all study groups when compared with baseline except for the adenosine 200 μg/kg/min group. However, these changes from baseline were not different among the groups. There were also no significant differences in PR, QRS, and QT intervals between the treatment groups.
Conclusion There was no difference in QTc prolongation following intraoperative administration of adenosine infusion compared with placebo during isoflurane general anesthesia. However, QTc prolongation is common following general anesthesia.

Keywords Adenosine · QTc · ECG · General anesthesia

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Introduction

Adenosine, a breakdown product of adenosine triphosphate (ATP), is involved in numerous biological processes including neurotransmission, muscle contraction, heart function, and antiinflammatory activity [1–4]. Recently, adenosine has been shown to be effective in treating neuropathic pain, hyperalgesia, and ischemic pain through receptor-mediated action in the spinal cord [5, 6]. At low

doses, adenosine has been found in some studies to reduce intraoperative anesthetic requirement and postoperative pain with minimal adverse effects [7–10].

QTc interval prolongation, associated with potential risk of serious arrhythmias, including torsades de pointes and ventricular fibrillation [11, 12], has become the most common reason for restrictive labeling of drugs [13]. Adenosine has been reported to prolong QTc interval in subjects with coronary artery disease and long QT syndrome [14, 15]. However, the impact of intraoperative administration of adenosine on QTc interval during general anesthesia is less clear. There were no previous studies specifically investigating the effect of intravenous adenosine infusion on QTc interval during and after general anesthesia. Therefore, as part of a multicenter, randomized, double-blind, placebo-controlled study to determine the dose response of adenosine for postoperative analgesia, we evaluated the impact of intravenous infusion of escalating doses of adenosine on QTc interval after general anesthesia. The null hypothesis is that an intraoperative continuous infusion of adenosine does not result in prolongation of QT interval.

Materials and methods

This multicenter study was approved by the institutional Review Board of the respective investigation sites, and all patients gave written informed consent. The study enrolled 166 female patients aged 18–60 years with American Society of Anesthesiologists (ASA) physical status I–III who were scheduled for elective open major gynecological surgery under general anesthesia.

Exclusion criteria included clinically significant cardiovascular diseases, history of asthma, gout, hepatic, renal, and endocrine disorders, positive pregnancy test or currently nursing infant, and obesity (body mass index >37 kg/m^2). Patients who were taking theophylline (or derivative), or dipyridamole within 48 h before surgery, or corticosteroids for longer than 3 months, patients with a history of chronic opioid use or current use within 14 days before surgery, and patients who had hypersensitivity to adenosine, morphine, or hydrocodone, were also excluded.

Subjects were randomly assigned to receive one of four doses of adenosine (25, 50, 100, or 200 μg/kg/min) or matching placebo based on a computer-generated random table. A dose-escalation cohort approach was followed. Standard anesthesia monitors including pulse oximeter, automated noninvasive blood pressure (NIBP), electrocardiogram (ECG), capnograph, and bispectral index (BIS) were applied during the intraoperative period. After premedication with midazolam 1–2 mg, anesthesia was induced with lidocaine up to 60 mg IV, propofol 1.5–2.5 mg/kg IV, and fentanyl 2 μg/kg IV. A muscle relaxant of the anesthesiologist's choice was used to facilitate tracheal intubation. General anesthesia was maintained with nitrous oxide (>50 % in oxygen) and isoflurane. Anesthesia was adjusted according to a predefined algorithm to maintain hemodynamic values [blood pressure (BP) and heart rate (HR)] within 25 % of baseline, and BIS value between 40 and 60. Blinded study medication (adenosine or matching normal saline placebo) was supplied in 500-ml glass bottles by the investigational pharmacists of each institution. Each bottle was identified by a unique number associated with active or placebo treatment. Bottle numbers were assigned by the interactive voice response system. To maintain blinding between the active and placebo groups, subjects were also assigned a specified infusion rate (in ml/kg) that was dependent upon the cohort under study. Infusion was initiated at the time of surgical incision through a dedicated peripheral intravenous catheter and discontinued at the time of skin closure. A baseline rhythm strip was obtained following intubation. Rhythm strips were repeated to document any ECG evidence of adverse cardiovascular events requiring intervention or interruption of study drug such as significant arrhythmias, conduction defects, or changes consistent with acute ischemia. In addition to intraoperative evaluation by the anesthesiologist, all rhythm strips were evaluated postoperatively by a cardiologist to assess for the occurrence of any ECG abnormalities. In the last cohort (200 μg/kg/min), the study drug was started at the corresponding 100 μg/kg/min rate, then increased by 25 μg/kg/min increments every 2–3 min, if the dose was tolerated. Immediately before each escalation in the dose of the study drug, a 6-s rhythm strip was obtained. If an adverse cardiovascular event or significant hemodynamic changes occurred during the gradual increase in dose, the dose was reduced back to the previously tolerated dose and maintained at that level throughout the procedure. No nonsteroidal antiinflammatory drug or corticosteroid was administered during surgery.

A baseline 12-lead ECG was obtained and repeated in the postanesthesia care unit (PACU) by a research personnel blinded to the patient's group. Values of QTc were calculated and recorded by the ECG device using the formula of Bazett ($QTc = QT/RR^{1/2}$) [16] and verified manually based on recommended guidelines [17]. QTc values >470 ms were considered to be clinically prolonged.[1] PR, QRS and QT intervals were also recorded. Electrocardiographic findings or cardiac adverse events were recorded

[1] Committee for Proprietary Medicinal Products: the assessment of the potential for QT interval prolongation by non-cardiovascular medical products. The European Agency for the Evaluation of Medicinal Products. Available at: http://www.emea.eu.int/pdfs/human/swp/098696en.pdf.

throughout the intra- and postoperative period by blinded research personnel. All the ECG recordings were assessed by a team comprising four anesthesiologists and a cardiologist before unblinding.

Statistical analysis

In addition to adequate sample size based on the primary outcome of the parent study, namely the consumption of morphine in the initial 24 h after surgery, the study was also sufficiently powered to demonstrate a change in QTc prolongation between the groups. Sample size estimation was based on the Duke perioperative ECG database with an assumption of 5 % change in the mean QTc interval of 440 ms with a standard deviation of 22 ms. Twenty-four patients per group were necessary to demonstrate such a difference with an alpha of 0.05 and beta of 0.9.

All data are presented as mean (SD) unless otherwise specified. SPSS 13.0 was used for data analysis. Comparison of the changes from baseline in QTc interval and other electrocardiographic data between treatment groups was performed by one-way repeated-measures analysis of variance (ANOVA) and, if significant, the Student–Newman–Keuls (SNK) test was applied for post hoc multiple comparisons. Paired-sample *t* test was used to compare the data within groups. All data were subjected to normality testing using the Kolmogorov–Smirnov test. A p value < 0.05 was considered statistically significant.

Results

The results of the main study, namely, postoperative analgesic response, have been presented elsewhere [18]. This article presents the data on ECG findings. A total of 166 patients participated in the study. Among them, 15 patients did not have electrocardiographic data either at baseline or after general anesthesia. A total of 151 patients had a full set of electrocardiographic data for analysis: placebo group ($n = 38$), group 1 (adenosine 25 μg/kg/min, $n = 31$), group 2 (adenosine 50 μg/kg/min, $n = 29$), group 3 (adenosine 100 μg/kg/min, $n = 28$), and group 4 (adenosine 200 μg/kg/min, $n = 25$).

All study groups were similar with respect to their demographic data including age, weight, duration of anesthesia, total dosages of analgesic and anesthetic drugs, and the time from the end of adenosine infusion to 12-lead ECG measurement after surgery (Table 1). Also, plasma electrolyte values were not different and found to be within normal ranges in all groups at preoperative and postoperative measurements.

Changes in heart rate (HR) and mean arterial pressure (MAP) are shown in Table 2. HR and MAP did not differ significantly between groups at baseline. There were also no significant differences between groups in MAP in the PACU. There were, however, significant differences between the groups in HR in the PACU ($p < 0.05$ for groups adenosine 50 μg/kg/min and 200 μg/kg/min versus placebo and adenosine 25 μg/kg/min) and in both MAP ($p < 0.05$ for groups adenosine 100 and 200 μg/kg/min versus placebo, and groups adenosine 25 and 50 μg/kg/min) and HR ($p < 0.05$ for groups adenosine 50, 100, and 200 μg/kg/min versus placebo and group adenosine 25 μg/kg/min) intraoperatively. Within-group comparisons showed significantly higher MAP postoperatively compared to baseline in all groups and intraoperatively compared to baseline in the placebo group, but significantly lower MAP intraoperatively compared to baseline in groups adenosine 100 and 200 μg/kg/min. There was no difference between baseline and PACU HR in all groups, but intraoperative HR was significantly higher

Table 1 Demographic data

	Placebo	Adenosine			
		Group 1 (25 μg/kg/min)	Group 2 (50 μg/kg/min)	Group 3 (100 μg/kg/min)	Group 4 (200 μg/kg/min)
N	38	31	29	28	25
Age (years)	44.5 (6.7)	47.8 (8.6)	46.9 (7.2)	45.4 (9.4)	46.0 (7.8)
Weight (kg)	78.3 (14.7)	73.8 (12.6)	74.7 (11.3)	75.4 (15.4)	76.2 (13.5)
Duration of anesthesia (min)	148.2 (60.4)	134.8 (75.5)	152.1 (61.1)	165.5 (75.5)	138.2 (50.1)
Time from end of infusion to postoperative ECG measurement (min)	84.8 (50.1)	94.2 (55.2)	108.0 (62.3)	84.4 (76.9)	74.4 (50.7)
Total propofol dose (mg)	163.0 (41.2)	158.1 (32.3)	164.3 (44.6)	172.9 (85.8)	145.8 (42.2)
Total fentanyl dose (μg)	319.1 (168.0)	258.6 (140.0)	288.6 (156.0)	284.5 (144.9)	258.6 (154.1)

Data presented as mean (SD)

Table 2 Heart rate and mean arterial pressure changes

Group	Time point	MAP	HR
Placebo	Baseline	77.2 (13.6)	75.8 (12.9)
	Intraop/Δ	85.1 (11.3)/8.0 (12.4)*	72.2 (11.8)/−3.6 (13.7)
	PACU/Δ	89.6 (12.0)/12.5 (16.1)*	72.3 (10.2)/−3.5 (14.2)
Cohort 1 (adenosine 25 μg/kg/min)	Baseline	81.8 (16.0)	76.6 (12.0)
	Intraop/Δ	82.0 (10.6)/0.2 (14.9)	72.1 (11.1)/−4.5 (11.1)*
	PACU/Δ	91.9 (12.7)/10.1 (17.9)*	74.9 (10.8)/−1.7 (14.4)
Cohort 2 (adenosine 50 μg/kg/min)	Baseline	79.7 (12.6)	78.5 (12.0)
	Intraop/Δ	79.5 (9.0)/0.3 (11.0)	82.6 (13.2)/4.1 (10.5)*
	PACU/Δ	92.0 (11.9)/12.0 (12.5)*	81.0 (13.8)/2.8 (14.4)
Cohort 3 (adenosine 100 μg/kg/min)	Baseline	77.6 (12.9)	75.4 (12.6)
	Intraop/Δ	68.6 (9.7)/−9.0 (10.7)*	80.2 (10.2)/4.8 (11.2)*
	PACU/Δ	89.7 (13.1)/12.2 (14.0)*	78.8 (13.6)/3.4 (14.3)
Cohort 4 (adenosine 200 μg/kg/min)	Baseline	78.8 (10.4)	81.5 (15.5)
	Intraop/Δ	68.8 (9.3)/−10.1 (14.6)*	87.3 (11.2)/5.8 (14.1)*
	PACU/Δ	92.6 (10.3)/13.3 (14.9)*	84.8 (11.1)/2.9 (16.2)

Data expressed as mean (SD)

MAP mean arterial pressure, *HR* heart rate, *Intraop* intraoperative, *PACU* postanesthesia care unit, Δ changes from baseline

Significantly different from the baseline, * $p < 0.05$

than baseline in groups adenosine 50, 100, and 200 μg/kg/min and lower than baseline in group adenosine 25 μg/kg/min.

There were no significant differences in electrocardiographic values at baseline between the study groups (Table 3). The QTc intervals were significantly prolonged in the postoperative period compared with baseline in all groups, except for group 4 (adenosine 200 μg/kg/min) (Table 4). However, there was no dose–response relationship in the degree of QTc prolongation. The maximum QTc prolongation was 92 ms in patients receiving adenosine at 100 μg/kg/min. The number of patients in whom the QTc interval exceeded the reference value of 470 ms more than doubled at the end of surgery when compared to baseline (Table 5). QTc value above 500 ms was found only in two patients receiving adenosine at 100 μg/kg/min.

Rhythm strips obtained during adenosine infusion showed first degree A-V block in one subject in the 100 μg/kg/min cohort with a PR interval of about 280 ms at a HR of 73 beats per minute (bpm), and in one subject in the 200 μg/kg/min cohort. In the latter subject, HR decreased during dose escalation from 100 bpm at a rate of 125 μg/kg/min to 75 bpm at the highest rate of 200 μg/kg/min. At the same time there was progressive prolongation of the PR interval, which was about 180 ms at a rate of 175 μg/kg/min and 250 ms at 200 μg/kg/min. One patient developed second-degree heart block during the dose escalation in the 200 μg/kg/min cohort; this occurred at the 200 μg/kg/min dose and was preceded by first-degree heart block with a PR interval prolonged up to 300 ms. Two subjects developed ST segment changes at the 200 μg/kg/min dose. A summary of adverse cardiovascular events is shown in Table 6 [18].

Discussion

There was no difference in the ECG changes, including QTc prolongation, between patients who received intraoperative infusion of adenosine 25–200 μg/kg/min and placebo. However, a high incidence of QTc prolongation after surgery was noted in this cohort of patients having major gynecological surgery under general anesthesia. QTc values increased significantly after surgery in all the study groups except those receiving adenosine 200 μg/kg/min.

The US Food and Drug Administration (FDA) has recently increased its focus on drug-related prolongation of QT interval. QTc value >450 ms in men and 470 ms in women is considered to be prolonged based on a report of the committee for proprietary medicinal products (London, UK). In our study, 17 % of patients receiving adenosine and 21 % of patients in the placebo group had an absolute QTc interval exceeding the upper threshold of 470 ms after anesthesia. Multiple factors can prolong QTc interval during the perioperative period [19–24]. Volatile anesthetics are known to cause QTc prolongation during anesthesia. Isoflurane has been found to prolong the QT interval in adults and children by activation of the sympathetic nervous system or increased plasma noradrenaline concentration [23, 24]. Other drugs commonly administrated perioperatively including antiemetics (e.g., droperidol, haloperidol, dolasetron, and ondansetron) [19], antihistamines (terfenadine), antibiotics (moxifloxacin), and antifungals (ketoconazole) are also known to prolong QTc interval [20]. Ondansetron 4 mg administrated in the present study may have contributed to the prolongation of QTc interval. A previous study [19] demonstrated almost uniform transient QTc prolongation following the

Table 3 ECG variables

	Placebo group			Adenosine											
				Group 1 (25 μg/kg/min)			Group 2 (50 μg/kg/min)			Group 3 (100 μg/kg/min)			Group 4 (200 μg/kg/min)		
	Baseline	PACU	Δ	Baseline	PACU	Δ	Baseline	PACU	Δ	Baseline	PACU	Δ	Baseline	PACU	Δ
PR (ms)	153.2 (23.1)	155.2 (23.2)	2.0 (20.6)	150.0 (15.0)	154.1 (13.4)	4.0 (12.1)	159.0 (20.3)	157.8 (22.4)	−1.2 (17.7)	156.3 (21.0)	154.1 (21.3)	−2.2 (12.1)	147.2 (18.3)	148.4 (16.0)	1.2 (12.7)
QRS (ms)	86.3 (8.0)	88.5 (8.7)	2.2 (5.0)	83.8 (6.4)	86.7 (6.8)	2.9 (4.7)	81.1 (7.9)	82.2 (9.5)	1.1 (6.4)	85.1 (10.4)	87.2 (8.9)	2.0 (8.5)	83.0 (7.7)	85.3 (9.1)	2.3 (6.1)
QT (ms)	407.4 (26.0)	413.0 (36.0)	5.6 (35.9)	385.2 (27.5)	397.9 (33.7)	12.8 (31.8)	389.5 (35.8)	394.8 (41.2)	5.3 (30.6)	411.5 (30.5)	415.3 (41.3)	3.7 (34.2)	426.4 (26.0)	386.0 (38.1)	−1.8 (36.2)

Data expressed as mean (SD)

PACU postanesthesia care unit, Δ changes from baseline

administration of ondansetron and droperidol, and the peak of QTc prolongation was about 5 min after drug administration. These parameters usually return to baseline within 20 min after drug administration is completed. As ondansetron was administered before induction in this study, it is unlikely that its effect persisted after surgery. We are not able to determine the principal cause of the prolongation of the QTc that we observed. Multiple drugs are likely to have caused the QT prolongation we document, including isoflurane, which was used during surgery.

Furthermore, other factors may contribute to QTc interval prolongation during the perioperative period such as pain, female sex, obesity, and electrolyte changes [12].

Several case reports have shown that adenosine administered by intravenous bolus may produce polymorphic ventricular tachycardia in patients with normal QTc interval or long QT syndrome. When used for a pharmacological stress test in patients with history of coronary artery disease, Guideri et al. [14] observed that adenosine administered at doses of 50–140 μg/kg/min produced QTc prolongation only in patients with a positive test, thus suggesting that significant QTc prolongation may be attributable to the development of myocardial ischemia rather than direct pharmacological effect of adenosine. However, in another study, Kern et al. [25] reported that adenosine infusion at 50–150 μg/kg/min did not induce QTc interval prolongation in patients with and without left coronary artery disease.

Adenosine administered intraoperatively as an analgesic appeared to be associated with few cardiovascular adverse events. Fukunaga et al. [10] observed no arrhythmias or other adverse cardiac effects when intravenous adenosine 50–500 μg/kg/min was administered during general anesthesia. However, the lack of reliable QTc data in patients treated with different doses of adenosine during anesthesia contributes to the controversy about its safe use in the perioperative period. In this study, we did not find any evidence that doses of adenosine up to 200 μg/kg/min administered intraoperatively were associated with clinically significant prolongation of QTc interval after general anesthesia compared with placebo. In two patients who received adenosine at 100 μg/kg/min, the absolute QTc value exceeded 500 ms. However, there was no evidence of any ectopic electrocardiographic activity. Interestingly, even at the maximum dose of 200 μg/kg/min of adenosine, QTc interval was not different when compared with placebo. We did not perform 12-lead ECG during the administration of adenosine due to practical reasons. We did not perform serial 12-lead ECG in the later postoperative period, so are unable to comment on the time of return of QTc to baseline.

An important limitation of our study is that the half-life of adenosine is short but the posttreatment ECGs were

Table 4 QTc values

	Placebo group	Adenosine			
		Group 1 (25 μg/kg/min)	Group 2 (50 μg/kg/min)	Group 3 (100 μg/kg/min)	Group 4 (200 μg/kg/min)
Baseline (ms)	424.0 (27.2)	411.7 (13.7)	423.0 (21.7)	431.4 (27.9)	426.4 (26.0)
PACU (ms)	444.3 (30.0)*	427.0 (22.7)*	435.9 (24.4)*	453.2 (34.9)*	436.7 (33.7)
Changes from baseline (ms)	20.24 (28.4)	15.35 (23.9)	12.90 (26.3)	21.79 (30.8)	10.3 (30.8)
p value	0.003	0.002	0.04	0.01	0.23

Data are mean (SD)

PACU postanesthesia care unit

* $p < 0.05$ compared with baseline

Table 5 Numbers and percentages of patients with QTc value above 470 ms

	Placebo group	Adenosine			
		Group 1 (25 μg/kg/min)	Group 2 (50 μg/kg/min)	Group 3 (100 μg/kg/min)	Group 4 (200 μg/kg/min)
Baseline	2 (5)	0 (0)	0 (0)	4 (14)	3 (12)
PACU	8 (21)	1 (3)	2 (7)	9 (32)	7 (28)

Data are *n* (%)

PACU postanesthesia care unit

Table 6 Adverse cardiovascular effects during adenosine infusion

	Placebo	Adenosine (25 μg/kg/min)	Adenosine (50 μg/kg/min)	Adenosine (100 μg/kg/min)	Adenosine (200 μg/kg/min)
First-degree AV block	0 (0)	0 (0)	0 (0)	1 (3)	1 (3)
Second-degree AV block	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
Bradycardia	1 (2)	0 (0)	0 (0)	1 (3)	1 (3)
ST segment depression	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)
T wave abnormality	0 (0)	0 (0)	1 (4)	2 (8)	0 (0)

Data are number (%)

obtained between 1 and 2 h after adenosine infusion, and only rhythm strips were obtained during the infusion; therefore, there could have been effects during the infusion that were not evident in the ECGs obtained in the PACU. The study was also not primarily designed to assess the effects of adenosine on the ECG. However, it is a large carefully conducted study that at least offers evidence of no discernible effect on QTc within 1 or 2 h after discontinuation of adenosine, and no generally adverse cardiac effects other than some evidence for expected AV conduction delay at higher doses; this provides more information than is otherwise currently available in the literature on adenosine.

Conclusion

QTc prolongation is common after isoflurane-based anesthesia. There was no difference in QTc interval between intraoperatively administered adenosine (up to 200 μg/kg/min) and placebo. There were some effects on PR interval with the higher doses of adenosine, as noted in intraoperative rhythm strips, consistent with the known effects of the drug.

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